



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁶ : A61M 5/32 | A1 | (11) International Publication Number: WO 97/25085 (43) International Publication Date: 17 July 1997 (17.07.97) |
| (21) International Application Number: PCT/US96/20932 (22) International Filing Date: 23 December 1996 (23.12.96) (30) Priority Data: 08/583,239 5 January 1996 (05.01.96) US (60) Parent Application or Grant (63) Related by Continuation US 08/583,239 (CIP) Filed on 5 January 1996 (05.01.96) (71) Applicant (for all designated States except US): COLUMBIA UNIVERSITY OF THE CITY OF NEW YORK [US/US]; Broadway & 116th Street, New York, NY 10027 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MODAK, Shanta [US/US]; 184 Howland Avenue, River Edge, NJ 07661 (US). SAMPATH, Lester [US/US]; 7 Lawrence Street, Nyack, NY 10960 (US). (74) Agents: TANG, Henry, Y., S. et al.; Brumbaugh, Graves, Donohue & Raymond, 30 Rockefeller Plaza, New York, NY 10112 (US). | (81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. | |
| (54) Title: TRICLOSAN-CONTAINING MEDICAL DEVICES (57) Abstract <p>The present invention relates to polymeric medical articles comprising the antinfecitive agents chlorhexidine and triclosan. It is based, at least in part, on the discovery that the synergistic relationship between these compounds permits the use of relatively low levels of both agents, and on the discovery that effective antimicrobial activity may be achieved when these compounds are comprised in either hydrophilic or hydrophobic polymers. It is also based on the discovery that chlorhexidine free base and triclosan, used together, are incorporated into polymeric medical articles more efficiently. Medical articles prepared according to the invention offer the advantage of preventing or inhibiting infection while avoiding undesirably high release of antinfecitive agent, for example into the bloodstream of a subject.</p> | | |

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DescriptionTRICLOSAN-CONTAINING MEDICAL DEVICES1. INTRODUCTION

This application is a continuation in part of United States Patent Application Serial No. 08/483,239, filed January 5, 1996.

5 2. BACKGROUND OF THE INVENTION

The present invention relates to medical devices comprising synergistic combinations of triclosan and chlorhexidine.

10 Whenever a medical device comes in contact with a patient, a risk of infection is created. Thus, a contaminated examination glove, tongue depressor, or stethoscope could transmit infection. The risk of infection dramatically increases for invasive medical devices, such as intravenous catheters, arterial
15 grafts, intrathecal or intracerebral shunts and prosthetic devices, which not only are, themselves, in intimate contact with body tissues and fluids, but also create a portal of entry for pathogens.

A number of methods for reducing the risk of
20 infection have been developed which incorporate anti-infective agents into medical devices, none of which have been clinically proven to be completely satisfactory. Such devices desirably provide effective levels of antiinfective agent during the entire period
25 that the device is being used. This sustained release may be problematic to achieve, in that a mechanism for dispersing antiinfective agent over a prolonged period of time may be required, and the incorporation of sufficient amounts of antiinfective agent may adversely
30 affect the surface characteristics of the device. The difficulties encountered in providing effective anti-

microbial protection increase with the development of drug-resistant pathogens.

One potential solution to these problems is the use of a synergistic combination of antiinfective agents that requires relatively low concentrations of individual antiinfective agents which may have differing patterns of bioavailability.

Two well-known antiinfective agents are chlorhexidine and triclosan. The following patents and patent application relate to the use of chlorhexidine and/or triclosan in medical devices.

United States Patent No.4,723,950 by Lee relates to a microbicidal tube which may be incorporated into the outlet tube of a urine drainage bag. The microbicidal tube is manufactured from polymeric materials capable of absorbing and releasing antimicrobial substances in a controllable sustained time release mechanism, activated upon contact with droplets of urine, thereby preventing the retrograde migration of infectious organisms into the drainage bag. The microbicidal tube may be produced by one of three processes: (1) a porous material, such as polypropylene, is impregnated with at least one microbicidal agent, and then coated with a hydrophilic polymer which swells upon contact with urine, causing the leaching out of the microbicidal agent; (2) a porous material, such as high density polyethylene, is impregnated with a hydrophilic polymer and at least one microbicidal agent; and (3) a polymer, such as silicone, is compounded and co-extruded with at least one microbicidal agent, and then coated with a hydrophilic polymer. A broad range of microbicidal agents are disclosed, including chlorhexidine and triclosan, and combinations thereof. The purpose of Lee's device is to allow the leaching out of microbicidal agents into urine contained in the drainage bag; similar

leaching of microbicidal agents into the bloodstream of a patient may be undesirable.

United States Patent No. 5,091,442 by Milner relates to tubular articles, such as condoms and catheters, which are rendered antimicrobially effective by the incorporation of a non-ionic sparingly soluble antimicrobial agent, such as triclosan. The tubular articles are made of materials which include natural rubber, polyvinyl chloride and polyurethane. Antimicrobial agent may be distributed throughout the article, or in a coating thereon. A condom prepared from natural rubber latex containing 1% by weight of triclosan, then dipped in an aqueous solution of chlorhexidine, is disclosed. United States Patents Nos. 5,180,605 and 5,261,421, both by Milner, relate to similar technology applied to gloves.

United States Patents Nos. 5,033,488 and 5,209,251, both by Curtis et al., relate to dental floss prepared from expanded polytetrafluoroethylene (PTFE) and coated with microcrystalline wax. Antimicrobial agents such as chlorhexidine or triclosan may be incorporated into the coated floss.

United States Patent No. 5,200,194 by Edgren et al. relates to an oral osmotic device comprising a thin semipermeable membrane wall surrounding a compartment housing a "beneficial agent" (that is at least somewhat soluble in saliva) and a fibrous support material composed of hydrophilic water-insoluble fibers. The patent lists a wide variety of "beneficial agents" which may be incorporated into the oral osmotic device, including chlorhexidine and triclosan.

United States Patent No. 5,019,096 by Fox, Jr. et al. relates to infection-resistant medical devices comprising a synergistic combination of a silver salt (such as silver sulfadiazine) and chlorhexidine.

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PCT/GB92/01481, Publication No. WO 93/02717, relates to an adhesive product comprising residues of a copolymerisable emulsifier comprising a medicament, which may be povidone iodine, triclosan, or chlorhexidine.

In contrast to the present invention, none of the above-cited references teach medical articles comprising synergistic combinations of chlorhexidine and triclosan which utilize relatively low levels of these agents.

3. SUMMARY OF THE INVENTION

The present invention relates to polymeric medical articles comprising the antiinfective agents chlorhexidine and triclosan. It is based, at least in part, on the discovery that the synergistic relationship between these compounds permits the use of relatively low levels of both agents, and on the discovery that effective antimicrobial activity may be achieved when these compounds are comprised in either hydrophilic or hydrophobic polymers. It is also based on the discovery that chlorhexidine free base and triclosan, used together, are incorporated into polymeric medical articles more efficiently. Medical articles prepared according to the invention offer the advantage of preventing or inhibiting infection while avoiding undesirably high release of antiinfective agent, for example into the bloodstream of a subject.

4. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to medical articles comprising synergistic combinations of chlorhexidine and triclosan.

5 Chlorhexidine may be provided by way of any form, salt or derivative thereof, including but not limited to chlorhexidine free base and chlorhexidine salts such as chlorhexidine diphosphanilate, chlorhexidine diglu-
10 conate, chlorhexidine diacetate, chlorhexidine dihydrochloride, chlorhexidine dichloride, chlorhexidine dihydroiodide, chlorhexidine diperchlorate, chlorhexidine dinitrate, chlorhexidine sulfate, chlorhexidine sulfite, chlorhexidine thiosulfate, chlor-
15 hexidine di-acid phosphate, chlorhexidine difluorophosphate, chlorhexidine diformate, chlorhexidine dipropionate, chlorhexidine di-iodobutyrate, chlorhexidine di-n-valerate, chlorhexidine dicaproate, chlorhexidine malonate, chlorhexidine succinate,
20 chlorhexidine malate, chlorhexidine tartrate, chlorhexidine dimonoglycolate, chlorhexidine monodiglycolate, chlorhexidine dilactate, chlorhexidine di- α -hydroxyisobutyrate, chlorhexidine diglucoheptonate, chlorhexidine di-isothionate, chlorhexidine dibenzoate,
25 chlorhexidine dicinnamate, chlorhexidine dimandelate, chlorhexidine di-isophthalate, chlorhexidine di-2-hydroxynapthoate, and chlorhexidine embonate. The term "chlorhexidine", as used herein, may refer to any of such forms, derivatives, or salts, unless specified
30 otherwise. Chlorhexidine salts may be solubilized using polyethylene glycol or propylene glycol, or other solvents known in the art.

The term triclosan refers to a compound also known as 2,4,4'-trichloro-2'-hydroxydiphenyl ether.

35 Medical articles that may be treated according to the invention are either fabricated from

or coated or treated with biomedical polymer and include, but are not limited to, catheters including urinary catheters and vascular catheters (e.g. peripheral and central vascular catheters), wound drainage tubes, arterial grafts, soft tissue patches, gloves, shunts, stents, tracheal catheters, wound dressings, sutures, guide wires and prosthetic devices (e.g. heart valves and LVADs). Vascular catheters which may be prepared according to the present invention include, but are not limited to, single and multiple lumen central venous catheters, peripherally inserted central venous catheters, emergency infusion catheters, percutaneous sheath introducer systems and thermodilution catheters, including the hubs and ports of such vascular catheters.

The present invention may be further applied to medical articles that have been prepared according to United States Patent No. 5,019,096 by Fox, Jr. et al.

The present invention provides, in various alternative nonlimiting embodiments, for: (1) compositions which provide a local concentration of chlorhexidine of between 100 and 2000 $\mu\text{g/ml}$ and a local concentration of triclosan of between 250 and 2000 $\mu\text{g/ml}$; (2) treatment solutions of a polymer comprising between 1 and 5 percent, and preferably between 1.5 and 2.25 percent, of chlorhexidine; and between .5 and 5 percent, and preferably between .5 and 2 percent, of triclosan, wherein a medical article may be dipped or soaked in the polymer solution; (3) medical articles treated with a treatment solution as set forth in (2) above, and articles physically equivalent thereto (that is to say, articles prepared by a different method but having essentially the same elements in the same proportions); (4) treatment solutions of a polymer comprising between 1 and 5 percent, and preferably between

1.5 and 2.25 percent, of chlorhexidine; between .5 and 5 percent, and preferably between .5 and 2 percent, of triclosan; and between .5 and 1 percent (preferably .75 percent) of silver sulfadiazine, wherein a medical
5 article may be dipped or soaked in the polymer solution; and (5) medical articles treated with a treatment solution set forth in (4) above, and articles physi-
cally equivalent thereto (that is to say, articles prepared by a different method but having essentially
10 the same elements in the same proportions). Percentages recited herein refer to percent by weight, except as indicated otherwise.

In preferred embodiments, the ratio, by weight, of the total amount of antiinfective agent to
15 polymer in the treatment solution is less than 1.5.

In one particular non-limiting embodiment, the present invention provides for a hydrophilic polymeric medical article (i.e., a medical article fabricated from a hydrophilic polymer) treated by
20 dipping or soaking the article in a treatment solution of a hydrophilic polymer comprising chlorhexidine and triclosan wherein the chlorhexidine and triclosan are present in amounts such that their combination, in the treated article, has effective antimicrobial activity.
25 The terms "treat", "treated", etc., as used herein, refer to coating, impregnating, or coating and impregnating a medical article with polymer/antiinfective agent. The term "hydrophilic polymer", as used herein, refers to polymers which have a water absorption
30 greater than 0.6 percent by weight (and, in preferred embodiments, less than 2 percent by weight; as measured by a 24 hour immersion in distilled water, as described in ASTM Designation D570-81) including, but not limited to biomedical polyurethanes (e.g. ether-based poly-
35 urethanes and ester-based polyurethanes, as set forth in Baker, 1987, in *Controlled Release of Biologically*

Active Agents, John Wiley and Sons, pp. 175-177 and Lelah and Cooper, 1986, *Polyurethanes in Medicine*, CRC Press, Inc., Fla. pp. 57-67; polyurethanes comprising substantially aliphatic backbones such as Tecoflex™

5 93A; polyurethanes comprising substantially aromatic backbones such as Tecothane™; and Pellethane™), polylactic acid, polyglycolic acid, natural rubber latex, and gauze or water-absorbent fabric, including cotton gauze and silk suture material. In a specific,

10 nonlimiting embodiment, the hydrophilic medical article is a polyurethane catheter which has been treated with (i.e., dipped or soaked in) a treatment solution comprising (i) between about 1 and 10 percent, preferably between about 2 and 6 percent, and more preferably

15 about 3 percent, of a biomedical polyurethane; (ii) between 1 and 5 percent, and preferably between 1.5 and 2.25 percent, of chlorhexidine; and (iii) between .5 and 5 percent, and preferably between .5 and 2 percent, of triclosan. In related nonlimiting embodiments of the

20 invention, the treatment solution may further comprise silver sulfadiazine, preferably in a concentration of between .5 and 1 percent (more preferably .75 percent). Section 6, below, presents working examples of embodiments set forth in this paragraph.

25 In another particular non-limiting embodiment, the present invention provides for a hydrophilic polymeric medical article treated by dipping or soaking the article in a treatment solution of a hydrophobic polymer comprising chlorhexidine and triclosan, wherein

30 the chlorhexidine and triclosan are present in amounts such that their combination, in the treated article, has effective antimicrobial activity. The term "hydrophobic polymer", as used herein, refers to a polymer which has a water absorption of less than 0.6% and

35 includes, but is not limited to, silicone polymers such as biomedical silicones (e.g., Silastic Type A) or

elastomers (e.g., as set forth in Baker, 1987, in *Controlled Release of Biologically Active Agents*, John Wiley and Sons, pp.156-162), Dacron, polytetrafluoroethylene (PTFE, also "Teflon"), polyvinyl chloride, cellulose acetate, polycarbonate, and copolymers such as silicone-polyurethane copolymers (e.g., PTUE 203 and PTUE 205 polyurethane-silicone interpenetrating polymer). In a specific, nonlimiting embodiment, the medical article is a polyurethane catheter which has been dipped or soaked in a treatment solution comprising (i) between about 1 and 10 percent, preferably between about 2 and 6 percent, and more preferably about 3 percent, of a polyurethane - silicone copolymer; (ii) between 1 and 5 percent, and preferably between 1.5 and 2.25 percent, of chlorhexidine; and (iii) between .5 and 5 percent, and preferably between .5 and 2 percent, of triclosan. In related nonlimiting embodiments of the invention, the treatment solution may further comprise silver sulfadiazine, preferably in a concentration of between .5 and 1 percent (more preferably .75 percent). Section 7, below, presents working examples of embodiments set forth in this paragraph.

In another particular non-limiting embodiment, the present invention provides for a hydrophobic polymeric medical article treated by dipping or soaking the article in a treatment solution of hydrophobic polymer comprising chlorhexidine and triclosan, wherein the chlorhexidine and triclosan are present in amounts such that their combination, in the treated article, has effective antimicrobial activity. In a specific, nonlimiting embodiment, the medical article is a silicone catheter or a polyvinylchloride catheter which has been dipped or soaked in a treatment solution comprising (i) between about 1 and 10 percent, and preferably about 5 percent, of a silicone polymer; (ii)

between 1 and 5 percent, and preferably between 1.5 and 2.25 percent, of chlorhexidine; and (iii) between .5 and 5 percent, and preferably between .5 and 2 percent, of triclosan. In related nonlimiting embodiments of the invention, the treatment solution may further comprise silver sulfadiazine, preferably in a concentration of between .5 and 1 percent (more preferably .75 percent). In still other related embodiments a coating of a hydrophobic polymer may be applied over the treated article. Section 8, below, presents working examples of embodiments set forth in this paragraph.

In another particular non-limiting embodiment, the present invention provides for a hydrophobic polymeric medical article treated by dipping or soaking the article in a treatment solution of hydrophilic polymer comprising chlorhexidine and triclosan, wherein the chlorhexidine and triclosan are present in amounts such that their combination, in the treated article, has effective antimicrobial activity. In a specific, nonlimiting embodiment, the medical article is a silicone catheter or Teflon graft which has been dipped or soaked in a treatment solution comprising (i) between about 1 and 10 percent, preferably between about 2 and 6 percent, and more preferably about 3 percent, of a biomedical polyurethane polymer; (ii) between 1 and 5 percent, and preferably between 1.5 and 2.25 percent, of chlorhexidine; and (iii) between .5 and 5 percent, and preferably between .5 and 2 percent, of triclosan. In related nonlimiting embodiments of the invention, the treatment solution may further comprise silver sulfadiazine, preferably in a concentration of between .5 and 1 percent (more preferably .75 percent).

Medical articles prepared according to the invention may be treated on their external surface, internal surface, or both. For example, and not by way of limitation, where the medical article is a catheter,

the internal surface and/or external surface of the catheter may be treated according to the invention. For example, where it is desired to treat both internal and external surfaces, an open-ended catheter may be placed in a treatment solution such that the treatment solution fills the catheter lumen. If only the external surface is to come in contact with treatment solution, the ends of the catheter may be sealed before it is placed in the treatment solution. If only the internal surface is to come in contact with treatment solution, the solution may be allowed to pass through and fill the lumen but the catheter is not immersed in the treatment solution.

Successful treatment of a medical article with a polymer comprising an antiinfective agent may be problematic, particularly where the medical article has a hydrophobic surface. The adherence of the polymer may depend upon (1) the polymeric matrix in which the antiinfective agent is suspended; (2) compatibility (or lack thereof) between the agent-polymeric matrix and the surface of the article; (3) the solvent system; and (4) the thickness of polymer/antiinfective agent desirably applied. Furthermore, the rates of release of various antiinfective agents from diverse polymers may differ. For example, the rate of release of chlorhexidine from a silicone matrix is faster than the rate of release of silver sulfadiazine from the same matrix. In order to compensate for this difference, one potential solution would be to increase the amounts of chlorhexidine and silver sulfadiazine in the matrix. Unfortunately, polymers comprising high levels of chlorhexidine and silver sulfadiazine have been found to adhere poorly to silicone catheters. In order to provide an alternative solution to the problem, two different methods for treating medical articles have

been developed: a one step method, and a two-step method, both of which are set forth below.

According to the one-step method of the invention, a polymeric medical article may be treated with a solution comprising one or more anti-infective agent, and optionally containing a biomedical polymer, dissolved in one or more solvents, wherein the solvent(s) selected are capable of swelling the polymeric medical article to be treated; such a solution is referred to herein as an "impregnating solution", and the process by which the article is treated with anti-infective agent is referred to as "impregnation". Suitable solvents include, but are not limited to, tetrahydrofuran ("THF"), dichloromethane, carbon tetrachloride, methanol, ethanol, methyl ethyl ketone, heptane, and hexane, and mixtures thereof. The biomedical polymer may be hydrophilic or hydrophobic, and includes the various polymers set forth above.

If a hydrophilic polymeric medical article is to be impregnated with chlorhexidine and triclosan, the impregnating solution may, in specific nonlimiting embodiments, comprise the following (percentages of solvents in this paragraph being volume/volume): (1) 95% ethanol; (2) 70% ethanol/30% water; (3) 50% ethanol/50% water; (4) 30% reagent alcohol/70% THF containing 2-3% of a biomedical polyurethane; (5) 90% reagent alcohol/10% THF; or (6) 100% reagent alcohol. Preferred soaking times vary between 5 minutes and 1 hour.

In specific, nonlimiting embodiments of the invention, a hydrophilic medical article such as a polyurethane catheter may be impregnated using a solvent mixture of 70-90% ethanol and 10-30% water and chlorhexidine and triclosan for between 10 and 60 minutes. The article may then be dried for 24-48 hours.

If a hydrophobic polymeric medical article is

to be impregnated with chlorhexidine and triclosan, the impregnating solution may, in specific nonlimiting embodiments, comprise the following (percentages of solvents in this paragraph being volume/volume): (1) 10% methanol /90% THF; (2) 10% ethanol/90% THF; (3) 30% methanol/70% THF; (4) 30% ethanol/70% THF; (5) 1-5 percent silicone polymer in 10% methanol/90% THF; (6) 1-5 percent silicone polymer in 10% ethanol/90% THF; (7) 1-2 percent polylactic acid in 10% methanol/90% THF; (8) 1-2 percent polylactic acid in 10% ethanol/90% THF; (9) 1-5 percent silicone polymer in 30% methanol/70% THF; (10) 1-5 percent silicone polymer in 30% ethanol/70% THF; (11) 1-2 percent polylactic acid in 30% methanol/70% THF; (12) 1-2 percent polylactic acid in 30% ethanol/70% THF; (13) 1-5 percent silicone polymer in 100% methyl ethyl ketone; and (14) 1-2 percent polyurethane in 30% ethanol/70% THF. For specific examples, see Section 15, below.

In specific embodiments, the impregnating solution comprises between 0.2 and 10 percent antiinfective agent and between 0.5 and 4 percent biomedical polymer.

The medical article, or a portion thereof, may be immersed in the impregnating solution to swell, after which the article may be removed and dried at room temperature until all solvent has evaporated and the article is no longer swollen. During the swelling process, antiinfective agent (and small amounts of polymer when present in the impregnating solution) may be distributed within the polymeric substrate of the article; during drying, the antiinfective agent and biomedical polymer (where present) may migrate somewhat toward the surface of the article. After drying, the article may be rinsed in either water or alcohol and wiped to remove any excess antiinfective agent and/or polymer at the surface. This may leave a sufficient

amount of antiinfective agent just below the surface of the article, thereby permitting sustained release of the agent over a prolonged period of time. Anti-infective agents which may be incorporated by this process include but are not limited to chlorhexidine, 5 triclosan, silver sulfadiazine, parachlorometaxylene, benzalkonium chloride, bacitracin, polymyxin, miconazole and rifampicin, as well as combinations thereof.

In preferred, nonlimiting embodiments of the invention, synergistic combinations of chlorhexidine 10 and triclosan may be dissolved in a mixture of methanol and tetrahydrofuran to produce an impregnating solution that may be used to render a silicone catheter anti-infective.

In one specific, nonlimiting example, the amount of chlorhexidine may be between 1 and 5 percent and preferably between 1.5 and 2.25 percent of the impregnating solution, and the amount of triclosan may be between .5 and 5 percent, and preferably between .5 20 and 2 percent. The resulting impregnating solution may further contain between 1 and 10 percent and preferably between 2 and 4 percent of a biomedical polymer such as a silicone polymer (e.g., Silastic Type A), polyurethane, or polycaprolactone. Specific examples of the one-step method are provided in Section 12 below. 25

According to the two-step method of the invention, the one-step method may be used to impregnate a medical article with antiinfective agent, and then the medical article may be dipped into a polymeric solution and dried. This method forms a polymeric 30 coating on the article and further controls the rate of release of antiinfective agent. When the two step method is practiced, the biomedical polymer may be omitted from the first soaking step. Optionally, an antiinfective agent may further be comprised in the polymeric coating. In a specific, nonlimiting example, 35

a silicone catheter may be dipped in a mixture of methanol and tetrahydrofuran containing between about 1 and 5 percent, and preferably between 1.5 and 2.25 percent, of chlorhexidine; between .5 and 5 percent and preferably between .5 and 2 percent of triclosan; and between 1 and 10 percent, and preferably between 2 and 4 percent, of a biomedical polymer (preferably a silicone polymer such as Silastic Type A) for about 30 minutes, dried, and then dipped in a higher concentration (but less than 10 percent) of biomedical polymer dissolved in a suitable solvent. For example, but not by way of limitation, a coating may be applied using a solution of 30% ethanol/70% THF containing 2-3 percent of a biomedical polyurethane, or a solution of 1-5 percent of Silastic Type A.

Alternatively, a hydrophilic medical article, such as a polyurethane catheter, may be impregnated with one or more antimicrobial agent and then coated with a polymer.

Examples of the two-step method are set forth in Sections 8, 16 and 17 below.

As set forth in Section 17, below, it has further been discovered that when medical articles were treated with mixtures of chlorhexidine free base and triclosan, uptake of chlorhexidine and triclosan was enhanced, and the antimicrobial activity of such articles was improved. While not desiring to be bound to any particular theory, it is believed that chlorhexidine free base and triclosan form a complex with improved solubility. The foregoing effect was observed when chlorhexidine free base and triclosan were combined in a respective molar ratio of 1:2; according to the invention, chlorhexidine free base and triclosan may be dissolved in a solvent or solvent system at chlorhexidine free base:triclosan molar ratios of 1:1 to 1:3. The total weight percent of chlorhexidine free

base plus triclosan is between 1 and 10 percent. The chlorhexidine free base and triclosan may be dissolved in a solvent system comprising water, alcohol, or tetrahydrofuran, and mixtures thereof, to produce an impregnating solution. In one specific, non-limiting example of the invention, a 1:2 ratio of chlorhexidine free base and triclosan may be dissolved in a solvent system which is 70 percent tetrahydrofuran and 30 percent reagent alcohol. A medical article, for example, a polyurethane article, may be impregnated with chlorhexidine free base/triclosan by immersing the article in such an impregnating solution so that the medical article swells without losing substantial structural integrity. After impregnation, the article may be dried, and then optionally coated with a polymeric solution, according to the two-step method set forth above.

Antiinfective medical articles prepared by other methods (e.g., extrusion, casting) but being otherwise substantially the same as articles produced by dipping or soaking, are within the scope of the claimed invention.

4.1 EXAMPLE: COMBINATIONS OF CHLORHEXIDINE AND TRICLOSAN EXHIBIT SYNERGISTIC ACTIVITY IN BACTERIAL CULTURES

Various concentrations of chlorhexidine diacetate ("CHA") and/or triclosan ("TC") were dispensed in 1.0 ml trypticase soy broth ("TSB") containing 20 percent bovine calf serum ("BCS") and inoculated with 10^7 colony-forming units ("CFU") of *Staphylococcus aureus*. After one minute, the cultures were diluted with drug-inactivating medium (1:100 dilution in LTSB drug inactivating medium, which is 5% Tween 80, 2% lecithin, 0.6% sodium oleate, 0.5% sodium thiosulfate, 0.1% protease peptone and 0.1% tryptone) and 0.2 ml of the diluted culture was subcultured on a

trypticase soy agar plate for the determination of colony counts. The results, shown in Table I, demonstrate the synergistic activity of combinations of chlorhexidine and triclosan. For example, whereas 500 micrograms per milliliter of CHA causes an approximately 17-fold decrease in CFU, and 500 micrograms per milliliter of triclosan causes an approximately 2400-fold decrease, the combination of these agents is associated with zero CFU, an at least 1×10^7 -fold decrease.

TABLE I

| 15 | Antiinfective CFU/ml <u>Agent</u> <u>Kill</u> | <u>Concentration (μg/ml)</u> | <u>(1 minute</u> |
|----|--|---|-------------------|
| | CHA | 2000 | 2.1×10^3 |
| 20 | CHA | 1000 | 5.0×10^4 |
| | CHA | 500 | 6.0×10^5 |
| 25 | TC | 500 | 4.2×10^3 |
| | TC | 250 | 2.0×10^5 |
| | CHA + TC | 2000 + 500 | 0 |
| 30 | CHA + TC | 2000 + 250 | 0 |
| | CHA + TC | 1000 + 250 | 0 |
| | CHA + TC | 500 + 500 | 0 |
| | CONTROL | | 1.0×10^7 |

35

4.2. EXAMPLE: COMBINATIONS OF CHLORHEXIDINE AND TRICLOSAN ARE MORE EFFECTIVE THAN COMBINATIONS OF CHLORHEXIDINE AND SILVER SULFADIAZINE WHEN APPLIED TO HYDROPHILIC CATHETERS

40

Polyurethane central venous catheters fabricated Of Tecoflex 93-A polyurethane were dipped in solutions containing 3 percent of a biomedical poly-

urethane (Tecoflex 93-A; "PU") and CHA, TC and/or silver sulfadiazine ("AgSD") dissolved in 30 percent ethanol and 70 percent tetrahydrofuran ("THF") (v/v) and air-dried. Bacterial adherence on these catheters was measured as follows. A 2 cm segment of dipped catheter was suspended in 3 ml TSB containing 10 percent BCS and incubated in a water bath shaker at 37° C. The media was changed daily. After 2 days the catheter segments were removed and transferred to fresh media containing 10⁶ CFU/ml of *Staphylococcus aureus* and incubated for 24 hours. The segments were removed, rinsed with saline, and then suspended in LTSB drug-inactivating medium and sonicated for 20 minutes to remove the adherent bacteria. Aliquots from the LTSB extract were then subcultured on trypticase soy agar plates to determine colony counts. The results are presented in Table II, and demonstrate that combinations of CHA and TC are superior in preventing bacterial adherence when compared with CHA alone or in combination with AgSD.

TABLE II

| Bacteria Coating | Adherent (CFU/ml) |
|---------------------------------------|----------------------|
| 3% PU + 2.5% CHA | 5 x 10 ⁴ |
| 3% PU + 1.5% CHA + 0.75% AgSD | 2 x 10 ⁴ |
| 3% PU + 1.5% CHA + 1% TC | 5 |
| 3% PU + 1.5% CHA + 0.75% AgSD + 1% TC | 40 |

In additional experiments, addition segments of the same type of polyurethane catheters coated with CHA, TC and/or AgSD were tested for the ability to produce zones of inhibition in trypticase soy agar plates seeded with 0.3 ml of 10⁶ CFU of *Staphylococcus aureus*, *Enterobacter cloacae*, *Candida albicans*, and *Pseudomonas*

aeruginosa. The coated catheter segments were placed vertically on the seeded plates, which were then incubated for 24 hours at 37° C before the zones of inhibition were measured. The results, shown in Table III, demonstrate the superior effectiveness of mixtures of chlorhexidine and triclosan.

TABLE III

| Organism | Coating*: A | Zone Of Inhibition (mm) | | | |
|--|-------------|-------------------------|------|------|--|
| | | B | C | D | |
| <i>S. aureus</i> | 14.5 | 15.0 | 13.0 | 16.5 | |
| <i>E. cloacae</i> | 9.0 | 12.0 | 7.5 | 3.0 | |
| <i>C. albicans</i> | 12.0 | 12.0 | 11.5 | 0 | |
| <i>P. aeruginosa</i> | 12.5 | 12.5 | 12.0 | 0 | |
| * coating A= 3% PU + 2.25% CHA | | | | | |
| coating B= 3% PU + 1.75% CHA + 0.5% TC | | | | | |
| coating C= 3% PU + 1.75% CHA + 0.5% AgSD | | | | | |
| coating D= 3% PU + 0.5% AgSD + 1.75% TC | | | | | |

4.3. EXAMPLE: HYDROPHILIC CATHETERS COATED WITH HYDROPHOBIC POLYMER COMPRISING CHLORHEXIDINE AND TRICLOSAN HAVE ANTIMICROBIAL ACTIVITY

The antimicrobial effectiveness of polyurethane central venous catheters (fabricated from Tecoflex 93-A polyurethane) coated with chlorhexidine diacetate and either triclosan or silver sulfadiazine in two polymeric coatings of differing water absorption were tested. The polymeric coatings, applied as set forth in Section 6 above, comprised either polyurethane 93A ("PU 93A"), a hydrophilic polyurethane having a water absorption of about 1-2 percent or polyurethane-silicone interpenetrating polymer ("PTUE 205") a hydrophobic silicone-polyurethane copolymer having a water absorption of only 0.4%. Antibacterial activity was measured by zones of inhibition, using methods as set

- forth in Section 6, above. The results, as regards antibacterial activity toward *Staphylococcus aureus*, *Enterobacter cloacae*, and *Candida albicans* at days 1 and 3 of culture, are shown in Tables IV, V and VI, respectively, and demonstrate that combinations of chlorhexidine diacetate and triclosan were effective when comprised in hydrophilic (PU 93A) as well as hydrophobic (PTUE 205) coatings.

TABLE IV

10

Antibacterial Activity Against *S. aureus*

| Coating | Zone of Inhibition (mm) | |
|---------------------|-------------------------|--------------|
| | <u>Day 1</u> | <u>Day 3</u> |
| 15 3% PTUE 205 + | | |
| 1.5% CHA + 1.5% TC | 16.0 | 11.0 |
| 3% PTUE 205 | | |
| 2% CHA + 0.75% AgSD | 14.5 | 11.0 |
| 20 3% PU 93A + | | |
| 1.5% CHA + 1.5% TC | 16.0 | 11.5 |
| 3% PU 93A + | | |
| 2% CHA + 0.75% AgSD | 14.5 | 11.0 |

25

TABLE V

Antibacterial Activity Against *E. cloacae*

| Coating | Zone of Inhibition (mm) | |
|---------------------|-------------------------|--------------|
| | <u>Day 1</u> | <u>Day 3</u> |
| 30 3% PTUE 205 + | | |
| 1.5% CHA + 1.5% TC | 12.0 | 6.0 |
| 3% PTUE 205 | | |
| 2% CHA + 0.75% AgSD | 8.5 | 0 |
| 35 3% PU 93A + | | |
| 1.5% CHA + 1.5% TC | 11.0 | 7.0 |
| 3% PU 93A + | | |
| 2% CHA + 0.75% AgSD | 7.0 | 0 |

TABLE VI

Antibacterial Activity Against C. albicans

| | | Zone of Inhibition (mm) | |
|----|---------------------|-------------------------|-------|
| | | Day 1 | Day 3 |
| 5 | <u>Coating</u> | | |
| | 3% PTUE 205 + | | |
| | 1.5% CHA + 1.5% TC | 11.0 | 7.0 |
| | 3% PTUE 205 | | |
| | 2% CHA + 0.75% AgSD | 12.0 | 9.5 |
| 10 | 3% PU 93A + | | |
| | 1.5% CHA + 1.5% TC | 12.5 | 7.0 |
| | 3% PU 93A + | | |
| | 2% CHA + 0.75% AgSD | 10.0 | 6.5 |

15 4.4. EXAMPLE: HYDROPHOBIC CATHETERS TREATED WITH
HYDROPHOBIC POLYMER COMPRISING CHLORHEXIDINE
AND TRICLOSAN HAVE ANTIMICROBIAL ACTIVITY

 Silicone central venous catheters fabricated
from Dow Corning Q7-4765A silicone polymer or Q7-4765B
20 silicone polymer were used to determine the effective-
ness of impregnation with hydrophobic polymers com-
prising chlorhexidine diacetate and triclosan on
hydrophobic substrates. The silicone catheters were
soaked for about 30 minutes in a solution of 5 percent
25 methanol and 95 percent THF (v/v) comprising (i) 2
percent medical adhesive Silastic Type A and (ii)
chlorhexidine diacetate and either triclosan or silver
sulfadiazine. The dipped catheters were dried and then
dipped in a solution of 5 percent methanol and 95 per-
30 cent THF (v/v) containing 5 percent Silastic Type A
("Sila"), and dried again. The catheter segments were
then tested for the production of zones of inhibition
on trypticase soy agar plates inoculated with *S. aureus*
or *E. cloacae*. The results are presented in Table VII.

TABLE VII

| | <u>Treatment</u> | Zone Of Inhibition (mm) | |
|----|-------------------------|-------------------------|-----------|
| | | <u>S. aureus</u> | <u>E.</u> |
| 5 | <u>cloacae</u> | | |
| | 2% Sila + 1.5% CHA + | | |
| | 0.5% TC, then 5% Sila | >50 | 21 |
| | 2% Sila + 1.5% CHA + | | |
| | 0.5% AgSD, then 5% Sila | 17 | 15 |
| 10 | | | |

4.5. EXAMPLE: TRICLOSAN EXHIBITS PROLONGED RELEASE FROM POLYMER COATINGS

Silicone central venous catheters fabricated from Dow Corning Q7-4765A silicone polymer or Q7-4765B silicone polymer were treated as set forth in Section 8, above, and then, immediately after drying, were extracted in dichloromethane/methanol/water (50%/25%/25%, v/v) in order to determine the amount of agent contained in the catheter segment tested (i.e., the uptake). To determine the rate of drug release, catheter segments were suspended in saline and incubated at 37° C for up to seven days; the saline was collected and replaced with fresh saline on the first day and every 48 hours thereafter, and the amount of drug present in the collected saline was measured. The results are presented in Table VIII.

TABLE VIII

| | <u>Treatment</u> <u>Day7</u> | Uptake ($\mu\text{g}/\text{cm}$) | Release ($\mu\text{g}/\text{cm}$) | | |
|----|--------------------------------------|---------------------------------------|-------------------------------------|-------------|-------------|
| | | | <u>Day1</u> | <u>Day3</u> | <u>Day5</u> |
| 5 | 2% SilA + 2% CHA, then 5% SilA | 60 | 28.0 | 4.1 | 3.1 |
| | | | | | 2.6 |
| 10 | 2% SilA + 2% TC, then 5% SilA | 1168 | 10.0 | 9.5 | 11.1 |
| | | | | | 11.4 |

Silicone catheters impregnated with Silastic

- 15 Type A comprising either 2% triclosan or 2% chlorhexidine diacetate were then tested for the ability to produce zones of inhibition on trypticase soy agar plates inoculated with *S. aureus*, *E. cloacae*, *C. albicans*, or *P. aeruginosa*. The results of these
- 20 experiments are shown in Table IX, and demonstrate that when higher concentrations of triclosan or chlorhexidine diacetate alone were used, triclosan-treated catheters were found to be equally or more effective than CHA-treated catheters.

TABLE IX

| | | Zones Of Inhibition (mm) | | | |
|----|----------------------|---|-------------|--|-------------|
| | Treatments: | <u>2%SilA + 2%CHA,</u> <u>then 5% SilA</u> | | <u>2%SilA + 2%TC,</u> <u>then 5% SilA</u> | |
| | | <u>Day1</u> | <u>Day3</u> | <u>Day1</u> | <u>Day3</u> |
| | <u>Organism</u> | | | | |
| 35 | <i>S. aureus</i> | 17.5 | 16.0 | >50 | >50 |
| | <i>E. cloacae</i> | 15.0 | 9.0 | 40.0 | 40.0 |
| | <i>C. albicans</i> | 13.5 | 6.0 | 13.0 | 13.0 |
| 40 | <i>P. aeruginosa</i> | 13.0 | 0 | 8.5 | 0 |

4.5. EXAMPLE: UPTAKE OF CHLORHEXIDINE AND TRICLOSAN IN PTFE GRAFTS

Arterial grafts fabricated from polytetrafluoroethylene ("PTFE") were cut into segments and impregnated with Silastic Type A comprising chlorhexidine diacetate or triclosan in 30% methanol/70% THF (v/v), in proportions set forth below. The treated grafts were then extracted with dichloromethane/methanol/water (50%/25%/25%, v/v), and the amounts of solubilized antiinfective agents were determined. Table X shows the uptake of agent by the treated grafts.

TABLE X

| | <u>Treatment</u> | <u>Agent Uptake (µg/cm)</u> |
|----|------------------|-----------------------------|
| 15 | 2% Sila + 2% CHA | 895 |
| | 2% Sila + 2% TC | 2435 |

4.6. EXAMPLE: ANTIMICROBIAL EFFECTIVENESS OF MEDICAL ARTICLES FABRICATED FROM TEFLON, DACRON OR NATURAL RUBBER LATEX AND IMPREGNATED WITH COMBINATIONS OF CHLORHEXIDINE AND TRICLOSAN

Chlorhexidine diacetate and either triclosan or silver sulfadiazine, in proportions set forth below, were dissolved in 5% methanol/95% THF (v/v). Segments of Dacron grafts, PTFE grafts, and natural rubber latex urinary catheters were then soaked in the resulting solutions for 15 minutes to impregnate the segments with antiinfective agents. This procedure allows the polymer substrates of the devices to incorporate antiinfective agent. The segments were then removed from the soaking solution, dried, rinsed with water, and wiped. The ability of the treated segments to produce zones of inhibition on trypticase soy agar plates inoculated with *S. aureus* and *E. cloacae* was then tested. The results, shown in Tables XI - XIII, demonstrate that the combination of chlorhexidine and

triclosan produced superior antimicrobial results compared to the combination of chlorhexidine and silver sulfadiazine.

TABLE XI

PTFE Graft

| | <u>Impregnating Solution</u> | Zone Of Inhibition (mm) | |
|----|------------------------------|-------------------------|-------------------|
| | | <u>S. aureus</u> | <u>E. cloacae</u> |
| 5 | 5% CHA + 0.5% TC | 37.0 | 22.0 |
| 10 | 1.5% CHA + 0.75% AgSD | 22.0 | 16.5 |

TABLE XII

Dacron Graft

| | <u>Impregnating Solution</u> | Zone Of Inhibition (mm) | |
|----|------------------------------|-------------------------|-------------------|
| | | <u>S. aureus</u> | <u>E. cloacae</u> |
| 20 | 5% CHA + 0.5% TC | >40 | 30.0 |
| 25 | 1.5% CHA + 0.75% AgSD | 26.0 | 27.0 |

TABLE XIII

Latex Catheter

| | <u>Impregnating Solution</u> | Zone Of Inhibition (mm) | |
|----|------------------------------|-------------------------|-------------------|
| | | <u>S. aureus</u> | <u>E. cloacae</u> |
| 30 | 5% CHA + 0.5% TC | 26.0 | 20.0 |
| 35 | 1.5% CHA + 0.75% AgSD | 18.0 | 12.0 |

4.7. EXAMPLE: ANTIMICROBIAL EFFECTIVENESS OF SILICONE CATHETERS PREPARED BY A ONE-STEP IMPREGNATION METHOD

Silicone catheters, as used in Example 8, were prepared by a one-step impregnation method as follows. Segments of the silicone catheters were soaked for about 30 minutes in impregnating solutions of 90% THF/10% methanol (v/v) containing 2% Silastic Type A,

- chlorhexidine, and either silver sulfadiazine or triclosan. The segments were then dried, and tested for their ability to produce zones of inhibition (at one and three days) in trypticase soy agar plates
- 5 inoculated with *S. aureus*, *E. cloacae*, *C. albicans*, and *P. aeruginosa*. The results, presented in Table XIV, demonstrate the effectiveness of chlorhexidine and triclosan-impregnated catheters.

TABLE XIV

10

| | | Zones Of Inhibition (mm) | | | |
|----|----------------------|-------------------------------|-------------|---------------------------------|-------------|
| 15 | Treatments: | 2%SilA + 1.5%CHA + 0.5% TC | | 2%SilA + 1.5%CHA + 0.5% AgSD | |
| | <u>Organism</u> | <u>Day1</u> | <u>Day3</u> | <u>Day1</u> | <u>Day3</u> |
| 20 | <i>S. aureus</i> | >40 | 39 | 17.5 | 13.5 |
| | <i>E. cloacae</i> | 21 | 21 | 15 | 8 |
| | <i>C. albicans</i> | 13.5 | 7 | 13.5 | 6 |
| 25 | <i>P. aeruginosa</i> | 13.5 | 6.5 | 13 | 0 |

- Additional formulations of impregnating solutions were tested for their ability to render the
- 30 same type of silicone catheter segments antiinfective against *C. albicans*, the microorganism which appeared to be inhibited only by relatively high amounts of antiinfective agent. The following impregnating solutions comprised chlorhexidine, triclosan and either
- 35 Silastic Type A, polycaprolactone, or no polymer in a 5% methanol/95%THF solvent. Table XV shows that when both polymer and antiinfective agent were comprised in the impregnating solution, higher antiinfective activity was achieved.

40

TABLE XV

| | <u>Impregnating Solution</u> | <u>Zone Of Inhibition (mm)</u> |
|----|---|--------------------------------|
| 5 | 4% SilA + 5% CHA + 1% TC | 12.0 |
| | 1% polycaprolactone + 5% CHA + 1% TC | 12.0 |
| 10 | No polymer, 5%CHA + 1% TC | 6.5 |

4.8. EXAMPLE: DIFFUSION OF ANTIINFECTIVE AGENTS
FROM MEDICAL ARTICLES TREATED WITH
IMPREGNATING SOLUTIONS WITH AND WITHOUT
POLYMER

- 15 The following impregnating solutions, "A" and "B", were used to impregnate segments of Dacron and PTFE grafts. The treated grafts were then rinsed with saline, and the amounts of antiinfective agent
- 20 incorporated into the grafts were determined, before and after rinsing, by extraction of antiinfective agent with dichloromethane/methanol/water (50%/25%/25%, v/v). The results, set forth in Table XVI, demonstrate that the addition of a polymer to the impregnating solution
- 25 produces a treated medical article which exhibits greater retention of antiinfective agent.
- Solution A: 1% polycaprolactone + 0.1% CHA + 0.02% TC, in 5% methanol/95% THF (v/v)
- 30 Solution B: 0.1% CHA + 0.02% TC, in 5% methanol/ 95% THF (v/v)

TABLE XVI

| | | <u>Drug Levels ($\mu\text{g}/\text{cm}$)</u> | | | |
|----|-------------------|---|----------|------------|----------|
| 5 | Solution: | Dacron Graft | | PTFE Graft | |
| | | <u>A</u> | <u>B</u> | <u>A</u> | <u>B</u> |
| | <u>Solution A</u> | | | | |
| 10 | Before rinsing | 392 | 548 | 73 | 90 |
| | After rinsing | 353 | 547 | 56 | 88 |
| 15 | <u>Solution B</u> | | | | |
| | Before Rinsing | 409 | 573 | 50 | 44 |
| | After rinsing | 132 | 553 | 24 | 44 |

4.9. EXAMPLE: DRUG UPTAKE AND RELEASE BY
HYDROPHILIC CATHETERS IMPREGNATED WITH
CHLORHEXIDINE OR TRICLOSAN

25 Polyurethane central venous catheter segments fabricated of Tecoflex 93-A polyurethane were impregnated with solutions "C", "D", "E", "F" and "G" set forth below by soaking the catheter segments for about two minutes followed by drying and rinsing with water.

30 Drug uptake was measured by extracting the impregnated catheter segments with dichloromethane/methanol/water (50%/25%/25% v/v). Drug release was measured over a period of six days by suspending the catheter segments in saline (one 2 cm segment in 2 ml saline), and agitated in a heated water bath at 37° C; the saline was

35 changed daily and drug release was measured as described above. The results are shown in Table XVII. Polyurethane, as set forth below, is Tecoflex 93-A polyurethane.

40 Solution C: 3% polyurethane +
3% CHA in 30% reagent alcohol/70% THF

Solution D: 3% polyurethane + 3% TC in 30%
reagent alcohol/70% THF

Solution E: 3% polyurethane + 2% CHA + 2% TC,
in 30% reagent alcohol/70% THF

Solution F: 2% CHA in 95% ethanol

Solution G: 3% CHA + 1% TC in 95% ethanol

TABLE XVII

| | Solu- tion | Drug | Uptake ($\mu\text{g}/\text{cm}$) | Drug Release ($\mu\text{g}/\text{cm}$) | | | | | |
|----|---------------|------|---------------------------------------|--|------|-----|-----|-----|-----|
| | | | | Day No. | | | | | |
| | | | | 1 | 2 | 3 | 4 | 5 | 6 |
| 15 | C | CHA | 197 | 78 | 36 | 20 | 2.6 | 0.8 | 0.8 |
| | D | TC | 300 | 0.4 | .13 | 0.1 | 0.1 | 0.1 | 0.1 |
| | E | CHA | 202 | 66 | 16.8 | 7.0 | 5.0 | 5.0 | 5.0 |
| 20 | | TC | 230 | 0.4 | 0.3 | <.1 | <.1 | <.1 | <.1 |
| | F | CHA | 254 | 15 | 9.6 | 7.8 | 2.5 | 2.5 | 2.5 |
| | G | CHA | 223 | 7.1 | 3.5 | 3.0 | 0.8 | 0.8 | 0.8 |
| 25 | | TC | 368 | <.1 | <.1 | <.1 | <.1 | <.1 | <.1 |

4.10. EXAMPLE: RELEASE OF CHLORHEXIDINE AND TRICLOSAN FROM IMPREGNATED SILICONE CATHETER SEGMENTS

Segments of silicone central venous catheters
fabricated from Dow Corning Q7-4765A silicone polymer
or Q7-4765B silicone polymer were impregnated with
either solution H or I by soaking for 30 minutes, and
then the release of drug was measured daily by methods
set forth above. The results of these measurements are
presented in Table XVIII.

Solution H: 2% SilA + 5% CHA in 10% methanol/90% THF
(v/v)

Solution I: 2% SilA + 5% CHA + 2% TC in
10% methanol/90% THF (v/v)

TABLE XVIII

| Solu- tion | Drug | Day1 | Day2 | Daily Release ($\mu\text{g}/\text{cm}$) | | |
|---------------|------|------|------|---|------|------|
| | | | | Day3 | Day4 | Day5 |
| H | CHA | 2.7 | 1.0 | 0.6 | 0.9 | 0.9 |
| I | CHA | 0.8 | 0.9 | 0.6 | 0.8 | 0.8 |
| | TC | 2.6 | 5.6 | 2.3 | 1.5 | 1.5 |

10

4.11. METHOD OF RENDERING POLYURETHANE
CATHETERS INFECTION-RESISTANT BY
IMPREGNATION WITH A SYNERGISTIC COMBINATION
OF CHLORHEXIDINE AND TRICLOSAN

15 A one-step method ("Method 1") and a two-step
method ("Method 2") were used to treat polyurethane
catheters.

Method 1: An entire polyurethane central
venous catheter assembly including the hub, extension
20 line and catheter body may be soaked in an alcoholic
solution containing chlorhexidine and triclosan for a
specific time period sufficient to impregnate these
elements with chlorhexidine and triclosan without
altering the integrity of the polyurethane substrate.
25 The following solvent systems and soaking times are
suitable. The concentrations of chlorhexidine and
triclosan range from 0.5-5%.

TABLE XIX.

| | <u>Solvent system</u> | <u>Soaking time</u> |
|----|--|---------------------|
| | 95% ethanol/ 5% water | 2 - 30 minutes |
| | 100% reagent alcohol | 2 - 30 minutes |
| 5 | 90% reagent alcohol/10% water | 5 - 60 minutes |
| | 80% reagent alcohol/20% water | 5 - 60 minutes |
| | 70% reagent alcohol/30% water | 10 - 60 minutes |
| | 90% ethanol/10% water | 5 - 60 minutes |
| | 80% ethanol/20% water | 5 - 60 minutes |
| 10 | 70% ethanol/30% water | 10 - 60 minutes |
| | 20% methanol/10% isopropanol /40% reagent alcohol /30% water | 10 - 60 minutes |

Selection of the solvent mixture depends on
 15 the type of polyurethane substrate and antimicrobials
 used for impregnation. After soaking, the catheter is
 rinsed in water for 24 to 48 hours to allow the
 catheter to regain its original integrity and size.

20 Method 2. A catheter impregnated with chlor-
 hexidine and triclosan according to Method 1 is then
 dipped in 70% THF/30% reagent alcohol/ 1-3% poly-
 urethane/ 1-3% chlorhexidine/ 1-3% triclosan.

25 Catheters prepared by Method 1 provide a
 relatively slow and steady release rate from the
 luminal surface and outer surface for a prolonged
 period of time. This pattern of drug release results
 from the relatively lower ratio of drug to poly-
 30 urethane matrix (0.015).

Catheters prepared by Method 2 exhibit
 biphasic drug release. The higher ratio of drug to
 polyurethane in the outer coating (1.3) permits an
 initial release of large amounts of drugs (which may
 35 inactivate bacteria entering through the skin at the
 time of insertion) followed by slow and steady release

of drug impregnated in the catheter by Method 1. The outer polyurethane coating acts as a barrier and permits the controlled release of drug over a prolonged period of time.

- 5 As specific examples, Tecoflex polyurethane catheters were prepared using the following method and then tested for antimicrobial efficacy in their luminal and outer surfaces:

10 i) catheters were soaked in 2% chlorhexidine dissolved in 100% reagent grade alcohol for 1 hour, rinsed in water, and dried for 24-48 hours ("Catheter C");

15 ii) catheters were soaked in 2% chlorhexidine + 2% triclosan dissolved in 100% reagent grade alcohol for 15 minutes, rinsed in water, and dried for 24-48 hours ("Catheter TC");

 iii) catheters were soaked in 2% triclosan in 70% reagent alcohol/30% water for 2 minutes, rinsed in water, and dried for 24-48 hours ("Catheter T");

20 iv) catheter C (above) was dipped in 3% polyurethane + 2% chlorhexidine dissolved in 70% THF/30% reagent alcohol ("Catheter C-C");

 v) catheter C (above) was dipped in 3% polyurethane + 2% chlorhexidine + 0.75% AgSD dissolved in 70% THF/30% reagent alcohol ("Catheter C-A");

25 vi) catheter T (above) was dipped in 2% chlorhexidine + 2% triclosan dissolved in 70% THF/30% reagent alcohol ("Catheter T-R");

 vii) catheter TC (above) was dipped in 2% chlorhexidine + 2% triclosan dissolved in 70% THF/30% reagent alcohol ("Catheter TC-R"); and

30 viii) catheter TC (above) was dipped in 2% chlorhexidine + 0.75% AgSD dissolved in 70% THF/30% reagent alcohol.

35 Trypticase soy agar plates were seeded with 10^5 CFU *Staphylococcus aureus*/ml and 0.5 cm segments of

catheter were embedded vertically. The plates were then incubated for 24 hours at 37°C and zones of inhibition were measured. The results are shown in Table XX.

TABLE XX.

| 5 | Catheter type (mm) | Zone of Inhibition | |
|----|-----------------------|--------------------|-------|
| | | Lumen | Outer |
| | <u>surface</u> | | |
| | C | 15 | 15 |
| 10 | T | 21 | 21 |
| | TC | 25 | 25 |
| | C-C | 15 | 18 |
| | C-A | 15 | 18 |
| | T-R | 21 | 25 |
| 15 | TC-R | 23 | 26 |
| | TC-A | 23 | 26 |

17. METHOD OF RENDERING POLYURETHANE CATHETERS
INFECTION-RESISTANT BY IMPREGNATION WITH A
SYNERGISTIC COMBINATION OF CHLORHEXIDINE
FREE BASE AND TRICLOSAN

It was further discovered that when catheters were coated using insoluble chlorhexidine free base and triclosan, a soluble chlorhexidine/triclosan complex was formed which improved the drug uptake and, therefore, the efficacy of the catheter.

Method 3: Catheters prepared by Method 1 (see Section 16) were dried for 24-72 hours and then their outer surfaces were dipped in a polyurethane solution (1-3% polyurethane dissolved in THF/alcohol). Catheters prepared by this method exhibited a large amount of drug release initially followed by a small but synergistically effective amount of drug release for a prolonged period of time.

Method 4: Followed the same procedure as Method 1, except that insoluble chlorhexidine free base (CHX) was solubilized with triclosan (1 molar CHX:2 molar triclosan ratio), which forms a complex with CHX. After soaking for 5-10 minutes the catheters were dried for 1-3 days and then the outer surface was dipped in

either a polyurethane solution alone (1-3% polyurethane) or a solution of polyurethane containing CHX and triclosan (TC).

When relatively soluble chlorhexidine salts such as chlorhexidine acetate (CHA) were used to impregnate catheters, the release was undesirably rapid. We investigated the use of CHX as a substitute for CHA. CHX is not soluble in water or alcohol but, surprisingly, we found that when it was combined in a 1:2 molar ratio with triclosan, an alcohol soluble complex formed.

The uptake of chlorhexidine from a solution containing CHX-TC complex was greater than that obtained from a CHA-TC solution despite a higher CHA concentration in the soaking solution. Due to higher chlorhexidine levels and higher rate of chlorhexidine release from the substrate resulting from impregnation with CHX-TC complex, the infection resistance of the catheters was greater than those containing only CHA.

Method 5: Same as method 4 but the soaking and outer coating solutions also contained soluble chlorhexidine acetate.

As specific examples, the following experiments were performed using Tecoflex catheters:

(1) Catheters were prepared according to Method 3. Specifically, catheters were soaked in 5% CHA + 1% TC dissolved in reagent alcohol for 10 minutes, dried for three days, and then the outer surface was dipped in 2.7% Tecoflex polyurethane dissolved in THF/reagent alcohol (70%/30%); the resulting catheters are referred to as type 1, and the polyurethane/THF/reagent alcohol solution is referred to as Solution J.

(2) A second group of catheters was prepared as in (1), but instead of using Solution J for the outer coating, another solution was used: 0.5% CHX +

0.5% TC + 2.7% polyurethane dissolved in 70%THF/30% reagent alcohol ("Solution K"). The resulting catheters are referred to as type 2.

(3) Catheters were prepared using Method 5.

5 Specifically, catheters were soaked in a solution containing 2% CHX + 2% CHA + 2% TC dissolved in reagent alcohol for 10 minutes, dried for 3 days and their outer surfaces were dipped in Solution J. The resulting catheters are referred to as type 3.

10 (4) Catheters were prepared as in (3) but were dipped in Solution K to produce an outer coating. The resulting catheters are referred to as type 4.

(5) Catheters were prepared according to Method 4. Specifically, catheters were soaked for 10
15 minutes in 3% CHX + 3% TC in reagent alcohol, dried for 3 days, and outer surface coated in Solution J. The resulting catheters are referred to as type 5.

(6) Catheters were prepared as in (5) but outer surface coated with Solution K. The resulting
20 catheters are referred to as type 6.

(7) Catheters were prepared according to Method 3. Specifically, catheters were soaked in a solution containing 5% CHA + 1% TC in reagent alcohol for 10 minutes, dried for 3 days and then outer surface
25 coated using Solution J. The resulting catheters are referred to as type 7.

(8) Catheters were prepared as in (7), except were outer surface coated with 2.7% polyurethane + 3% CHA in 70% THF/ 30% reagent alcohol. The resulting
30 catheters are referred to as type 8.

Segments of catheter types 1-8 were placed vertically in inoculated trypticase soy agar plates inoculated with 10^8 CFU of *Staphylococcus aureus* per plate, and incubated for 24 hours. After measuring the
35 zones of inhibition, the catheters were transferred daily to fresh culture plates (shown in Table XXI).

TABLE XXI.

| | <u>Catheter type</u> <u>(mm)</u> | <u>Day</u> | <u>Zone of Inhibition</u> |
|----|-------------------------------------|------------|---------------------------|
| 5 | 1 | 21 | 12.0 |
| | 2 | 21 | 13.0 |
| | 3 | 21 | 17.0 |
| | 4 | 21 | 20.0 |
| | 5 | 21 | 20.0 |
| 10 | 6 | 21 | 23.0 |
| | 7 | 21 | 5.0 |
| | 8 | 21 | 9.0 |

The amount of drug uptake per cm/catheter in catheters prepared using various soaking solutions was measured as set forth above.

TABLE XXII.

| | <u>Soaking Solution</u> | <u>Drug Uptake/cm catheter</u> | |
|----|-------------------------|--------------------------------|------------------|
| 20 | | <u>Chlorhexidine</u> | <u>Triclosan</u> |
| | 5% CHA | 260-310[$\mu\text{g??}$] | --- |
| | 5% CHA + 2% TC | 280-300 | 450-480 |
| 25 | 2% CHX + 2% TC + 2% CHA | 480-520 | 300-370 |
| | 3% CHX + 3% TC | 550-660 | 600-700 |

The luminal adherence of bacteria was quantified in catheters impregnated with antimicrobials and then coated with a solution of 2.7 percent Tecoflex 93A and various antimicrobial agents. Bacteriol adherence was measured as follows. 12 cm segments of test and control 7Fr catheters were each connected to an individual channel of a peristaltic pump via an extension line, hub, and injection cap. The hubs were inoculated initially and after 24 hours with 10^6 cfu of *S. aureus* which causes the extension line to become colonized thus acting as a continuous source of bacteria for seeding lumens. The lumens were continuously perfused at a rate of 20ml/hour with trypticase soy broth (TSB) diluted 1:10 with physiological saline over the course of 7 days. At the end of one week the

catheter segments were disconnected and their outer surfaces disinfected with 70% ethanol. Each lumen was flushed with sterile TSB to remove non-adherent bacteria. Each catheter was then cut into 2 cm segment
 5 each of which is further divided into 2 mm subsegments and placed in tubes containing 4 ml of antiseptic inactivating broth (LTSB). The tubes were sonicated for 20 minutes at 4°C to remove bacteria adhering to the lumens. To quantify the adherence, a 0.5 ml
 10 aliquot of the LTSB extract was subcultured on trypticase soy agar plates. The results are shown in Table XXII.

TABLE XXIII.

| | DRUG IN <u>SOAKING SOLUTION</u> <u>(cfu/cm)</u> | DRUG IN <u>OUTER COATING</u> | BACTERIAL ADHERENCE <u>IN LUMEN</u> |
|----|---|---------------------------------|--|
| 15 | 5% CHA | 3% CHA | 3×10^4 |
| | 5% CHA + 0.5% TC | 2% CHA + 2% TC | 3×10^2 |
| 20 | 2% CHX + 2% CHA + 2% TC | 2% CHA + 2% TC | 0 |
| | 3% CHX + 3% TC | 0.5% CHX + 0.5% TC | 0 |
| | 0 (control) | 0 | 4×10^6 |
| 25 | 2% CHX + 2% CHA + 2% TC | no outer coating | 5 |

Various publications are cited herein, which are hereby incorporated by reference in their entireties.

WHAT IS CLAIMED IS:

1. A hydrophilic polymeric medical article which has been treated with a treatment solution comprising (i) between about 1 and 10 percent of a hydrophilic polymer; (ii) between 1 and 5 percent of an antiinfective agent selected from the group consisting of chlorhexidine free base, a chlorhexidine salt, and a chlorhexidine derivative; and (iii) between .5 and 5 percent of triclosan.
2. The medical article of claim 1 which is fabricated from a hydrophilic polymer selected from the group consisting of natural rubber latex and biomedical polyurethane.
3. The medical article of claim 1 wherein the hydrophilic polymer in the treatment solution is a biomedical polyurethane.
4. The medical article of claim 2 wherein the hydrophilic polymer in the treatment solution is a biomedical polyurethane.
5. A hydrophilic polymeric medical article having a coating comprising a hydrophilic polymer, triclosan, silver sulfadiazine, and an antiinfective agent selected from the group consisting of chlorhexidine free base, a chlorhexidine salt, and a chlorhexidine derivative, wherein the triclosan, silver sulfadiazine and antiinfective agent are present in amounts such that their combination, in the article, has effective antimicrobial activity.
6. The medical article of claim 5 which is a catheter.

7. The catheter of claim 6 which is an intravenous catheter.

8. The catheter of claim 7 which is
5 fabricated from a biomedical polyurethane.

9. The catheter of claim 8 wherein the hydrophilic polymer in the coating is a biomedical polyurethane.

10
10. A hydrophilic polymeric medical article treated with a treatment solution comprising a hydrophobic polymer, triclosan, and an antiinfective agent selected from the group consisting of
15 chlorhexidine free base, a chlorhexidine salt, and a chlorhexidine derivative, wherein the triclosan and antiinfective agent are present in amounts such that their combination, in the treated article, has effective antimicrobial activity.

20
11. The medical article of claim 10, further comprising silver sulfadiazine.

12. The medical article of claim 10 wherein
25 the hydrophobic polymer is a biomedical silicone polymer.

13. The medical article of claim 11 wherein the hydrophobic polymer is a biomedical silicone
30 polymer.

14. The medical article of claim 10 wherein the hydrophobic polymer is a silicone-polyurethane copolymer.

35

15. The medical article of claim 11 wherein the hydrophobic polymer is a silicone-polyurethane copolymer.

5 16. The medical article of claim 10 which is a catheter.

 17. The catheter of claim 16 which is an intravenous catheter.

10 18. The catheter of claim 17 which is fabricated from a biomedical polyurethane.

 19. The catheter of claim 18 wherein the
15 hydrophobic polymer in the solution is a biomedical silicone-polyurethane copolymer.

 20. A hydrophilic polymeric medical article which has been treated with a treatment solution
20 comprising (i) between about 1 and 10 percent of a hydrophobic polymer (ii) between 1 and 5 percent of an antiinfective agent selected from the group consisting of chlorhexidine free base, a chlorhexidine salt, and a chlorhexidine derivative; and (iii) between .5 and 5
25 percent of triclosan.

 21. The medical article of claim 20 which is fabricated from a hydrophilic polymer selected from the group consisting of natural rubber latex and biomedical
30 polyurethane..

 22. The medical article of claim 20 wherein the hydrophobic polymer in the treatment solution is a biomedical silicone polymer.

35

23. The medical article of claim 21 wherein the hydrophobic polymer in the treatment solution is a biomedical silicone polymer.

5 24. The medical article of claim 20 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

 25. The medical article of claim 21 wherein
10 the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

 26. A hydrophobic polymeric medical article treated with a treatment solution comprising a
15 hydrophobic polymer, triclosan, and a an antiinfective agent selected from the group consisting of chlorhexidine free base, a chlorhexidine salt, and a chlorhexidine derivative, wherein the triclosan and antiinfective agent are present in amounts such that
20 their combination, in the treated article, has effective antimicrobial activity.

 27. The medical article of claim 26, further comprising silver sulfadiazine.
25

 28. The medical article of claim 26 wherein the medical article is fabricated from a hydrophobic polymer selected from the group consisting of polytetrafluoroethylene, Dacron, polyvinylchloride and
30 a silicone polyurethane copolymer.

 29. The medical article of claim 27 wherein the medical article is fabricated from a hydrophobic polymer selected from the group consisting of
35 polyvinylchloride, polytetrafluoroethylene, Dacron and a silicone polyurethane copolymer.

30. The medical article of claim 26 wherein the medical article is fabricated from a silicone polymer.

5 31. The medical article of claim 27 wherein the medical article is fabricated from a silicone polymer.

32. The medical article of claim 26 wherein
10 the hydrophobic polymer in the treatment solution is a biomedical silicone polymer.

33. The medical article of claim 27 wherein the hydrophobic polymer in the treatment solution is a
15 biomedical silicone polymer.

34. The medical article of claim 26 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.
20

35. The medical article of claim 27 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

25 36. The medical article of claim 26 which is a catheter.

37. The catheter of claim 36 which is an intravenous catheter.
30

38. The catheter of claim 37 which is fabricated from a biomedical silicone polymer.

39. The catheter of claim 38 wherein the
35 hydrophobic polymer in the treatment solution is a biomedical silicone polymer.

40. A hydrophobic polymeric medical article which has been treated with a treatment solution comprising (i) between about 1 and 10 percent of a hydrophobic polymer (ii) between 1 and 5 percent of an
5 antiinfective agent selected from the group consisting of chlorhexidine free base, a chlorhexidine salt, and a chlorhexidine derivative; and (iii) between .5 and 5 percent of triclosan.

10 41. The medical article of claim 40 which is fabricated from a hydrophobic polymer selected from the group consisting of polytetrafluoroethylene, Dacron, polyvinylchloride, biomedical silicone polymer, and
silicone polyurethane copolymer.

15 42. The medical article of claim 40 wherein the hydrophobic polymer in the treatment solution is a biomedical silicone polymer.

20 43. The medical article of claim 41 wherein the hydrophobic polymer in the treatment solution is a biomedical silicone polymer.

25 44. The medical article of claim 40 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

30 45. The medical article of claim 41 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

46. A method for rendering a silicone catheter antiinfective, comprising:

35 (1) placing the silicone catheter in an impregnating solution comprising (a) a solvent which causes the catheter to swell; (b) between 1 and 5

percent of an antiinfective agent selected from the group consisting of chlorhexidine free base, a chlorhexidine salt, and a chlorhexidine derivative; (c) between .5 and 5 percent of triclosan; and (d) between 5 1 and 10 percent of a biomedical polymer;

(2) soaking the catheter in the impregnating solution for a period of time sufficient to allow the catheter to swell;

(3) removing the catheter from the 10 impregnating solution; and

(4) drying the catheter.

47. The method of claim 46, wherein the 15 biomedical polymer is a biomedical silicone polymer.

48. The method of claim 46, further comprising the step of dipping the catheter, after drying according to step (4), into a second coating solution comprising a biomedical polymer. 20

49. The method according to claim 48, wherein the biomedical polymer in both the impregnating solution and the second coating solution is a biomedical silicone polymer. 25

50. A hydrophobic polymeric medical article which has been treated with a treatment solution comprising (i) between about 1 and 10 percent of a hydrophilic polymer; (ii) between 1 and 5 percent of an 30 antiinfective agent selected from the group consisting of chlorhexidine free base, a chlorhexidine salt, and a chlorhexidine derivative; and (iii) between .5 and 5 percent of triclosan.

51. The medical article of claim 50 which is 35 fabricated from a hydrophobic polymer selected from the

group consisting of polytetrafluoroethylene, Dacron, polyvinylchloride, biomedical silicone polymer, and silicone polyurethane copolymer.

5 52. The medical article of claim 50 wherein the hydrophilic polymer is a biomedical polyurethane.

 53. A medical article which has been treated by a method comprising:

10 (1) placing the medical article in an impregnating solution comprising (a) a solvent selected from the group consisting of water, reagent alcohol, tetrahydrofuran, and mixtures thereof; and (b) chlorhexidine free base and triclosan, in a molar ratio
15 between 1:1 to 1:3, wherein the total weight of chlorhexidine free base and triclosan is between 1 and 10 percent of the weight of the impregnating solution;

 (2) soaking the catheter in the impregnating solution for a period of time sufficient to allow the
20 medical article to swell;

 (3) removing the medical article from the impregnating solution; and

 (4) drying the medical article.

25 54. The medical article of claim 53, wherein the solvent in step (1)(a) is a mixture of reagent alcohol and tetrahydrofuran.

 55. The medical article of claim 53, wherein
30 the ratio of chlorhexidine free base and triclosan in step (1)(b) is about 1:2.

 56. The medical article of claim 53, wherein
35 the total weight percent of chlorhexidine free base and triclosan in step (1)(b) is about 2-10.

57. The medical article of claim 53, which has further been coated with a coating solution comprising a biomedical polymer.

5 58. The medical article of claim 57, wherein the biomedical polymer in the coating solution comprises an antimicrobial agent.

59. The medical article of claim 53 which is
10 fabricated from polyurethanes.

60. The medical article of claim 59 which is a polyurethane catheter.

15 61. The medical article of claim 60 in which both the external and internal surfaces of the catheter are brought into contact with the impregnating solution.

20 62. The medical article of claim 60 in which only the external surface of the catheter is brought into contact with the impregnating solution.

63. The medical article of claim 60, in
25 which only the internal surface of the catheter is brought into contact with the impregnating solution.

64. A method of preparing an infection resistant medical article comprising:

30 (1) placing the medical article in an impregnating solution comprising (a) a solvent selected from the group consisting of water, reagent alcohol, tetrahydrofuran, and mixtures thereof; and (b) chlorhexidine free base and triclosan, in a molar ratio
35 between 1:1 and 1:3, wherein the total weight of

chlorhexidine free base and triclosan is between 1 and 10 percent of the weight of the impregnating solution;

(2) soaking the catheter in the impregnating solution for a period of time sufficient to allow the
5 medical article to swell;

(3) removing the medical article from the impregnating solution; and

(4) drying the medical article.

10 65. The method of claim 64, wherein the solvent in step (1)(a) is a mixture of reagent alcohol and tetrahydrofuran.

66. The method of claim 64, wherein the
15 ratio of chlorhexidine free base and triclosan in step (1)(b) is about 1:2.

67. The method of claim 64, wherein the total weight percent of chlorhexidine free base and
20 triclosan in step (1)(b) is about 2-10.

68. The method of claim 64, which has further been coated with a coating solution comprising a biomedical polymer.
25

69. The method of claim 68, wherein the biomedical polymer in the coating solution comprises an antimicrobial agent.

30 70. The method of claim 64 which is fabricated from polyurethane.

71. The method of claim 70 which is a polyurethane catheter.
35

72. The method of claim 71 in which both the external and internal surfaces of the catheter are brought into contact with the impregnating solution.

5 73. The method of claim 71 in which only the external surface of the catheter is brought into contact with the impregnating solution.

74. The method of claim 71, in which only
10 the internal surface of the catheter is brought into contact with the impregnating solution.

75. The medical article of claim 53 wherein
the impregnating solution of step (1) further comprises
15 chlorhexidine acetate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20932

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A51M 5/32

US CL : 604/265

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/265

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

428/35.7, 36.9; 604/264; 606/76

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | US 5,102,401 A (LAMBERT et al.) 07 April 1992. entire document | 10-13, 16-18 |
| Y | | 14, 15, 19-23 |
| Y | US 5,019,096 A (FOX, JR. et al.) 28 May 1991. entire document | 1-52 |
| Y | US 5,091,442 A (MILNER) 25 February 1992. entire document | 20-23 |
| Y | US 5,180,605 A (MILNER) 19 January 1993. entire document | 1-52 |

☒ Further documents are listed in the continuation of Box C. ☐ See parent family annex.

| | | |
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| "P" documents published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search

11 MARCH 1997

Date of mailing of the international search report

27 MAR 1997

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20932

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | US 5,165,952 A (SOLOMAN et al.) 24 November 1992. | 46-49, 53-75 |